

Changing Epidemiology of Human Brucellosis, China, 1955–2014

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Brucellosis, a zoonotic disease, was made statutorily notifiable in China in 1955. We analyzed the incidence and spatial–temporal distribution of human brucellosis during 1955–2014 in China using notifiable surveillance data: aggregated data for 1955–2003 and individual case data for 2004–2014. A total of 513,034 brucellosis cases were recorded, of which 99.3% were reported in northern China during 1955–2014, and 69.1% (258, 462/374, 141) occurred during February–July in 1990–2014. Incidence remained high during 1955–1978 (interquartile range 0.42–1.0 cases/100,000 residents), then decreased dramatically in 1979–1994. However, brucellosis has reemerged since 1995 (interquartile range 0.11–0.23 in 1995–2003 and 1.48–2.89 in 2004–2014); the historical high occurred in 2014, and the affected area expanded from northern pastureland provinces to the adjacent grassland and agricultural areas, then to southern coastal and southwestern areas. Control strategies in China should be adjusted to account for these changes by adopting a One Health approach.

Brucellosis is a bacterial zoonosis caused by *Brucella* spp., which can be transmitted from animal reservoirs,

such as cattle, sheep, goats, and pigs, to humans through direct contact with infected animals or ingestion of unpasteurized animal products (1–3). The global epidemiology of brucellosis has drastically changed over the past decades, particularly in industrialized countries where the disease was previously endemic but is now mainly associated with returning travelers. However, brucellosis remains a serious concern in low- and middle-income countries, which have most new human cases globally (estimated ≈500,000 cases annually) and major economic losses in animal production resulting from the adverse effects of infection on livestock reproduction (2,4,5). Additionally, human brucellosis is of particular concern because of high initial treatment failure, substantial residual disability of infected patients, and relapse rates (1,6). Moreover, *Brucella* spp. are highly infectious through the aerosol route, making them a potential agent of biological weapons and bioterrorism (7).

In China, brucellosis was first recorded as Malta fever for 2 foreigners in Shanghai in 1905, but several patients in China who had similar clinical symptoms had been observed in the 10 years before this report (8). After this report, 3 cases were reported from Chongqing in 1906 (9). The first person with a definite diagnosis of *Brucella* infection by serologic tests was reported from Fujian in 1916 (10). Subsequently, *Brucella* sp. was isolated from a foreigner and his goats who traveled from Punjab, India, to Henan Province, China, in 1925 (11), and human infection in a laboratory setting was reported in Beijing in 1936 (12). Thus, human brucellosis was seen in China before 1950, especially in the northern provinces (13).

Since 1950, activities for prevention and control of brucellosis have been gradually introduced in mainland China (14,15). During 1950–1963, the reporting for human brucellosis was established nationwide, and some surveys were conducted. Vaccination for animals and humans was implemented as the main control measure during 1964–1976 in regions with severe epidemics, such as Inner Mongolia, Xinjiang, Qinghai, Ningxia, and Henan Provinces (14). During 1977–1988, a national program for brucellosis control was conducted with the introduction of diagnostic criteria, treatment protocols, and control measures, and

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vaccination of domestic animals was used as the main control measure. National sentinel surveillance was established in 1990 to monitor the seroprevalence of brucellosis in humans and animals (16).

During the past decade, outbreaks of human brucellosis have been reported in increasing numbers and with an apparent geographic expansion from the historically affected north of China (17,18) to southern provinces where non-occupational exposure might be more common because of the increasing movement of humans, animals, and animal food products from brucellosis-endemic regions (19–21). The epidemiology of human brucellosis clearly presented major challenges in China during the past 60 years, but studies reporting the spatial–temporal patterns of human brucellosis with high-quality, nationwide incidence data are lacking (2,4,14,22,23). We describe the magnitude and distribution of human brucellosis in mainland China using the notifiable reporting data for 1955–2014 and emphasize its recent reemergence. Improving our understanding of the changing epidemiology of brucellosis and identifying high-risk areas can help in formulating plans for national strategies to prevent and control brucellosis.

Methods

Data Source and Ethical Considerations

On July 5, 1955, human brucellosis was made statutorily notifiable in China: all probable or laboratory-confirmed new brucellosis cases were required to be reported (online Technical Appendix Table 1, <https://wwwnc.cdc.gov/EID/article/23/3/16-1710-Techapp1.pdf>). In this study, we used 2 datasets because the requirements for reporting changed during the study period (24). One comprises the number of brucellosis cases aggregated by case-patient sex, age group, and occupation; incidence rate; death rate; and case-fatality ratio (online Technical Appendix Table 2), reported monthly through paper-based post or electronic files during 1955–2003. The other consists of individual brucellosis cases reported by doctors within 24 hours after diagnosis to the online National Notifiable Infectious Disease Reporting Information System at the Chinese Center for Disease Control and Prevention during 2004–2014. (Variables in individual datasets are available in online Technical Appendix Table 3.) All data used in this study were anonymized so that individual patients could not be identified.

The National Health and Family Planning Commission of China determined that the collection of data from human cases of brucellosis was part of continuing public health surveillance of a notifiable infectious disease and was exempt from institutional review board assessment. All data were supplied and analyzed in an anonymous format, without access to personal identifying information.

Case Definition

Brucellosis cases have been classified as probable (clinically diagnosed) or confirmed (laboratory confirmed) in accordance with the guidelines for human brucellosis diagnosis issued by the Chinese national health authorities in 1977, 1988, 1996, and 2007, which were successively used during 1977–2014 (online Technical Appendix Table 4). Probable cases are diagnosed by local experienced physicians according to patient anamnesis, epidemiologic exposure, clinical manifestations, and/or positive results of presumptive laboratory tests, including the plate agglutination test and the intradermal allergic reaction test. Confirmed cases are probable cases with 1 positive result of the following tests: standard tube agglutination test, complement fixation test, Coombs test, cysteine test for serologic diagnosis, or positive *Brucella* spp. isolation (1).

Data Analysis

Our analysis comprised all probable and confirmed cases in persons with illness onset from January 1, 1955, through December 31, 2014. According to the National Mid-term and Long-term Animal Disease Control Plan of China (25), all the provinces in northern China were identified as the key regions for brucellosis control. Therefore, we aggregated the surveillance data of each province to northern and southern China (online Technical Appendix Table 5), as previously reported (26), to examine spatial–temporal patterns by region. To eliminate the potential effect of the introduction of Internet-based reporting on the increasing number of cases since 2004, we made a time-series prediction of the number of cases in 2004 on the basis of data for 1993–2003, using the Holt exponential smoothing method with a 95% CI (27). Then we compared the upper value of the 95% CI with the actual number of cases in 2004 to calculate the excess proportion of cases that might have contributed to improved data reporting. Adjusted incidence rates for 2004–2014 were estimated by using this excess proportion and plotted as an epidemic curve. We also predicted the monthly numbers of cases during the next 5 years (2015–2019) by Holt-Winters exponential smoothing on the basis of data reported during 2004–2014 to explore the trend of incidence with seasonality (27).

We created a heat map of the yearly incidence rate to visualize the long-term change over the 60-year period by province. We also created a heat map of the monthly number of cases reported during 2005–2014 by province, standardized by the yearly number in each province, and plotted a heat map of average weekly proportions of case numbers by province to explore the seasonal pattern during 2005–2014. To test the differences between northern and southern China, we used Mann-Whitney U tests with a significance level of $\alpha = 0.05$ to test for differences in the time from illness onset to diagnosis and χ^2 with a significance

level of $\alpha = 0.05$ to test the differences in the proportion of imported cases. The *R* statistical software (version 3.1.2, R Foundation for Statistical Computing, Vienna, Austria) with the package *forecast* (version 6.1), was used to produce the graphs and heat maps and to perform statistical analyses and prediction, and *ArcGIS* 10.2.2 (ESRI, Redlands, CA, USA) was used to plot the geographic patterns.

Results

Demographic Features

During 1955–2014, a total of 513,034 human brucellosis cases (median 3,504/year [interquartile range (IQR) 1,145–7,886]), including 170 deaths, were reported to the national human brucellosis surveillance system in mainland China (Figure 1, panel A). Among them, 346,682 (67.6%) cases were reported in the individual database during 2004–2014; the proportion of laboratory-confirmed cases ranged from 76.9% in 2004 to 93.2% in 2014 (Table; Figure 2). Most cases during 2004–2014 occurred in males; the male:female ratio was 2.9:1 for both northern (2.9:1)

and southern (2.6:1) China (Table; online Technical Appendix Table 6). Median age of case-patients was 44 years (IQR 34–54 years), and case distribution was similar by sex and type of diagnosis and between northern and southern China (Figure 2). Most (88.8%) case-patients were farmers or veterinarians or worked in livestock husbandry, transportation, and trade or food production during 2004–2014.

Overall Incidence and Seasonality

The annual incidence rate fluctuated during the 60 years studied (Figure 1, panel A). Before 1979, human brucellosis incidence was relatively steady (IQR 0.4–1.0 cases/100,000 residents) and peaked during 1957–1963 (range 0.9–1.8/100,000) and again during 1969–1971 (range 1.0–1.2/100,000). Incidence decreased dramatically beginning in 1979 and remained low until 1994 (IQR 0.05–0.10/100,000). However, the incidence increased from 1995 through 2014 (median 0.2/100,000 [IQR 0.1–0.2] during 1995–2003 and 2.5/100,000 [IQR 1.5–2.9] during 2004–2014); incidence was highest (4.2 cases/100,000 residents) in 2014. After removal of the excess proportion

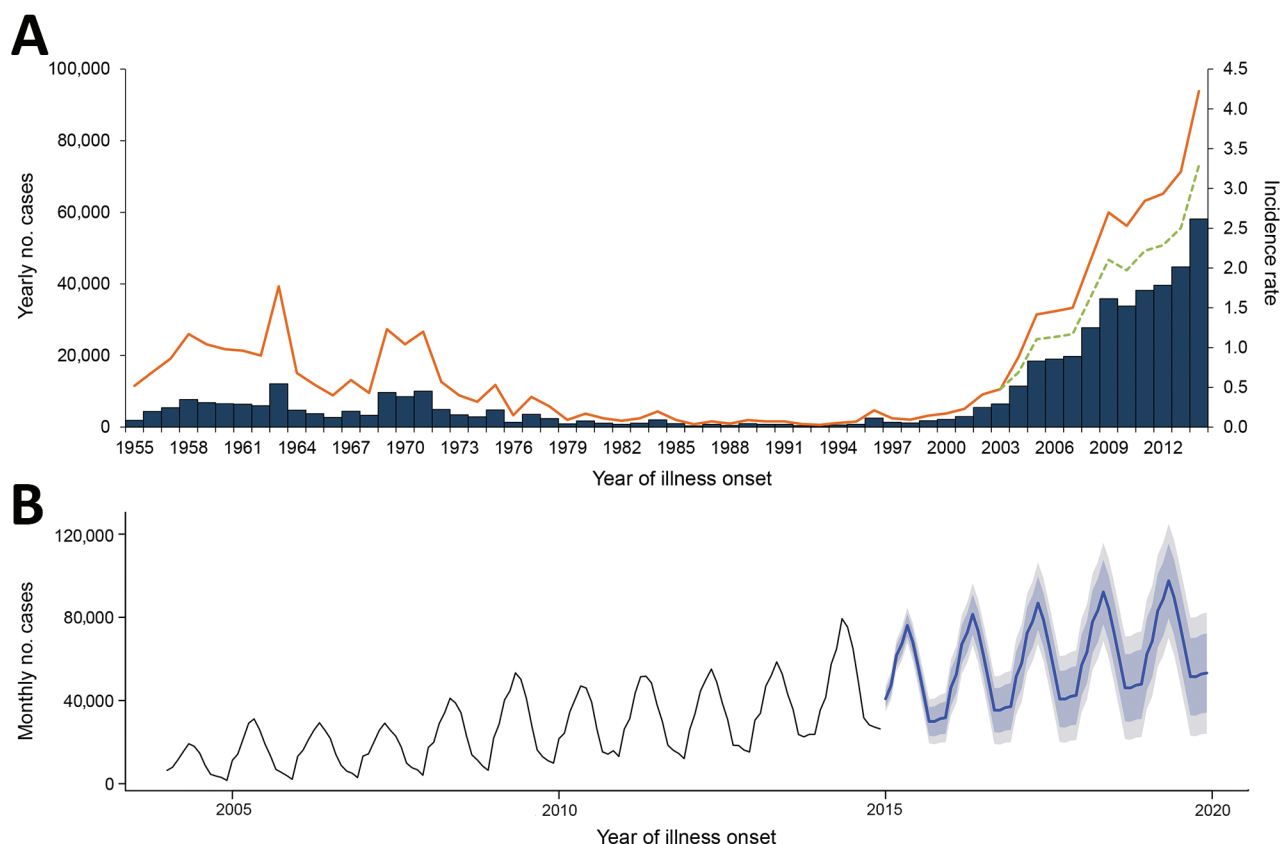


Figure 1. Reported human brucellosis cases ($N = 513,034$), mainland China, 1955–2014. A) Aggregated number of cases (blue bars) and annual incidence rate (orange line) per 100,000 residents reported by year. The adjusted incidence rate (green dashed line) was estimated by an excess proportion (22.06%) that might be attributed to the effect of Internet-based reporting since 2004 (see Methods). B) Forecast of the monthly number of cases (blue line) during 2015–2019 by Holt-Winters exponential smoothing with 80% CIs (light gray) and 95% CIs (dark gray) based on monthly numbers for 2004–2014.

Table. Characteristics of persons with brucellosis, mainland China, 2004–2014*

Characteristic	Total, N = 346,682	Northern China, n = 344,204	Southern China, n = 2,478
Type of case			
Confirmed	314,694 (90.8)	312,371 (90.8)	2,323 (93.7)
Probable	31,988 (9.2)	31,833 (9.2)	155 (6.3)
Sex			
M	42,912 (73.8)	42,166 (73.9)	746 (71.0)
F	15,230 (26.2)	14,926 (26.1)	304 (29.0)
Age, y			
Median (IQR)	44.0 (34.1–53.9)	44.0 (34.1–53.9)	46.6 (36.6–56.1)
Age group			
0–4	2,424 (0.7)	2,402 (0.7)	22 (0.9)
5–14	6,638 (1.9)	6,596 (1.9)	42 (1.7)
15–24	25,262 (7.3)	25,108 (7.3)	154 (6.2)
25–34	57,651 (16.6)	57,313 (16.7)	338 (13.6)
35–44	90,777 (26.2)	90,209 (26.2)	568 (22.9)
45–54	87,566 (25.3)	86,901 (25.2)	665 (26.8)
55–64	57,274 (16.5)	56,765 (16.5)	509 (20.5)
≥65	19,090 (5.5)	18,910 (5.5)	180 (7.3)
Median delay, d (IQR)			
From illness onset to diagnosis	20.0 (7.5–42.0)	20.0 (7.5–42.0)	20.7 (8.5–47.5)
From diagnosis to report	0.25 (0.04–0.65)	0.25 (0.04–0.65)	0.15 (0.04–0.66)
From illness onset to report	20.6 (7.8–43.4)	20.6 (7.8–43.4)	19.5 (8.0–44.7)
Origin of imported case			
Same county	205,941 (59.4)	204,912 (59.5)	1,029 (41.5)
Other county of same prefecture	92,351 (26.6)	91,628 (26.6)	723 (29.2)
Other prefecture of same province	32,584 (9.4)	32,088 (9.3)	496 (20)
Other province	15,806 (4.6)	15,576 (4.5)	230 (9.3)

*The list of provinces in northern and southern China is available in online Technical Appendix Table 5, <https://wwwnc.cdc.gov/EID/article/23/3/16-1710-TeChapp1.pdf>. Data are presented as no. (%) patients unless otherwise indicated. IQR, interquartile range.

(22.1%; online Technical Appendix Figure 1) to account for the potential effect of improvements in data reporting since 2004, the adjusted incidence rate still indicated an average annual growth rate of 20.8% during 2003–2014, and it appears that brucellosis incidence will continue to rise during the next 5 years (Figure 1, panel B). Additionally, 69.1% (258,462/374,141) of the cases were reported in February–July during 1990–2014, with an obvious seasonality in northern China in 2005–2014 (Figure 3).

Geographic Distribution

Most (99.3%) cases were reported in northern China during 1955–2014, and most provinces in northern China experienced a serious epidemic during the 1950s through the 1970s. Incidence subsequently decreased from the late 1970s through the early 1990s and the disease reemerged in the mid-1990s with cases reported almost every year (Figure 3; online Technical Appendix Figure 2). The 5 provinces with the highest median incidence rates during 1955–1994 were Tibet (14.07 cases/100,000 residents), Qinghai (4.43), Shanxi (0.87), Xinjiang (0.35), and Inner Mongolia (0.35); during 1995–2014, highest incidences shifted to Inner Mongolia (25.80), Shanxi (7.33), Heilongjiang (6.07), Jilin (1.79), and Hebei (1.40).

Similarly, the incidence in southern China has increased since 2000, and human brucellosis has emerged or reemerged in all provinces of southern China. Cases have been reported in almost every province and year since 2010. This finding contrasts with the distribution of brucellosis

before 2000, when the disease was limited to a few provinces in southern China, such as Sichuan, Guangxi, and Guangdong (Figures 3, 4; online Technical Appendix Figure 2). Additionally, the proportion of imported cases was higher in southern than northern China (58.5% vs. 40.5%; $p < 0.001$), but cases in southern China had a longer lag from illness onset to diagnosis than did those in northern China (21 vs. 20 days; $p = 0.003$) (Table).

Correspondingly, the number of counties reporting human cases in mainland China increased from 87 in 1993 to 1,723 in 2014; each year since 2004, hundreds of counties were newly affected (Figures 5, 6). The proportion of counties affected in southern China increased from 1.1% in 2004 to 20.5% in 2014, highlighting the spatial spread over the past decade. From a land cover perspective, during 2004–2014, affected areas seem to have expanded from the provinces in northern pastureland areas to the adjacent grassland and agricultural areas that have a high density of sheep and goats, then to coastal areas and southeastern China (Figure 6).

Discussion

We used a longitudinal surveillance dataset spanning 60 years in China to investigate changes in the epidemiologic characteristics of human brucellosis, especially during the period of dramatic socioeconomic changes during the past 3 decades, during which the urban population increased from 19% in 1980 to 54% in 2014 (30). Human brucellosis has reemerged in mainland China since the mid-1990s;

incidence has increased and the disease has expanded geographically from northern to southern China. Our study, with long-term and high-quality incidence data, complements a previously published map of human brucellosis in East Asia (2–4).

The temporal trend in human brucellosis incidence in this study (i.e., high incidence during 1955–1978, low incidence during 1979–1994, and high (and increasing) incidence from 1995 onwards) is consistent with the trend

in *Brucella* spp. seroprevalence from animal and human serosurveys conducted in China during 1950–2014. An overall seroprevalence of 41.27% in cattle, sheep, and pigs in brucellosis-endemic areas and 8.43% in humans was reported for 1952–1981, but seroprevalence was only 0.55% in animals and 0.75% in humans during 1982–1990 after implementation of a national control program in 1979 (14,31). During 1990–2001, seroprevalence in humans was 3.28% and has increased steadily since 1995, despite the

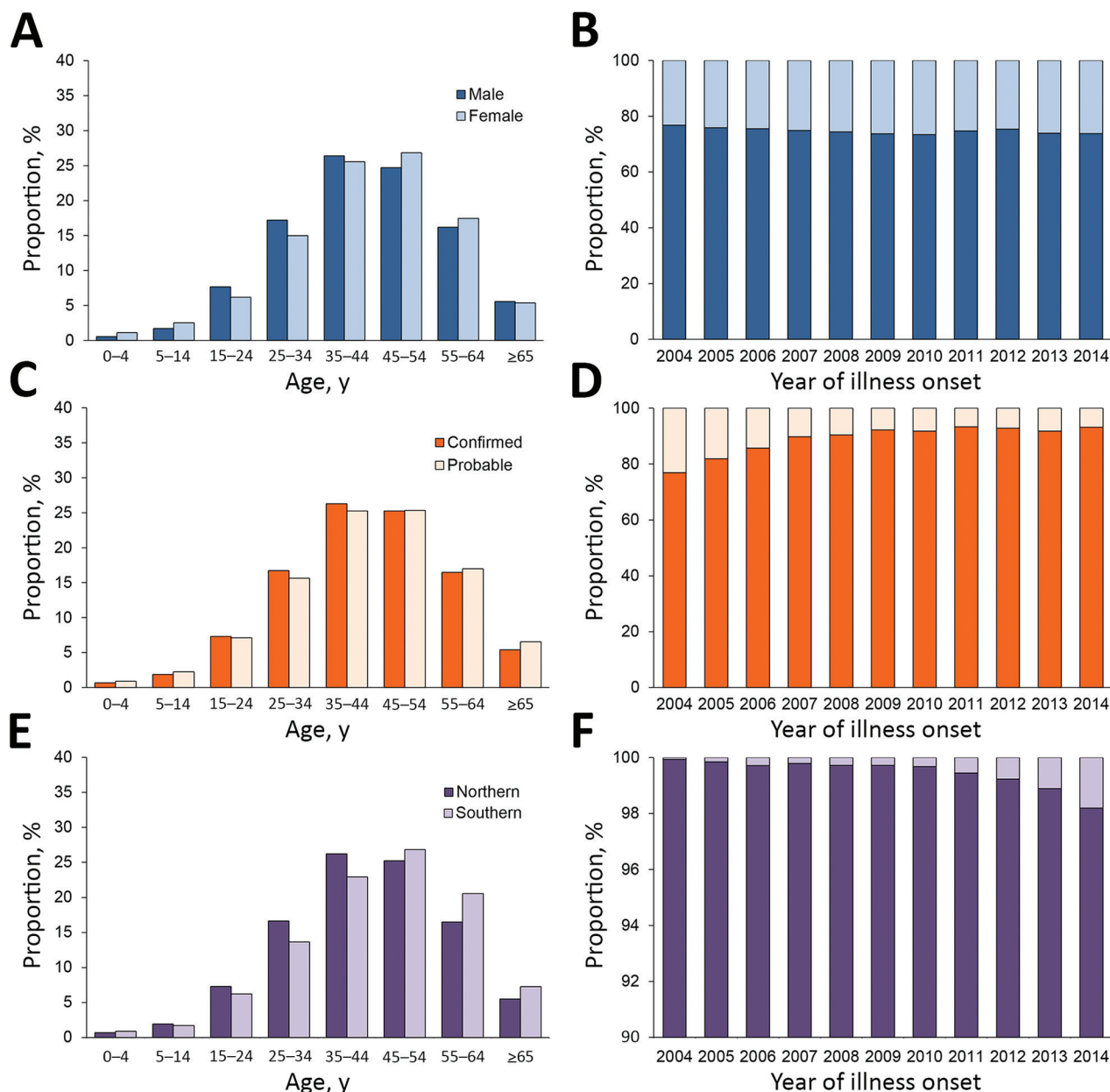


Figure 2. Age distribution and proportion of 346,682 human brucellosis patients, mainland China, 2004–2014. A) Age distribution by sex. B) Annual proportion of patients by sex. C) Age distribution of persons with probable and confirmed cases. D) Annual proportion of probable and confirmed cases. E) Age distribution of patients in northern and southern China. F) Proportion of cases in northern and southern China each year.

lack of obvious change in domestic animals (0.36%) (16). In the 21st century, seroprevalence maintained an increasing trend in occupationally exposed populations (11.36% during 2001–2004, 13.31% during 2005–2006, 21.97% in 2007, and 22.75% in 2011) and livestock (0.28% during 2001–2004, 0.72% during 2005–2006, and 1.49% in sheep in 2009) (32–35). Although incidence appeared to increase in every province, Tibet seems to follow an inverse pattern and reported few cases during the past 10 years, but serologic surveys indicate that seroprevalence of *Brucella* infection in animals and humans remained high in some areas since 2005 (36). Additionally, this study found a low case-fatality rate in passive surveillance, and the poor follow-up for outcomes of human brucellosis with chronic infection and illness might have contributed.

After brucellosis reemerged in China, the geographic distribution of affected areas gradually expanded (14). The areas of brucellosis endemicity gradually shifted from pasturing areas (i.e., Inner Mongolia, Xinjiang, Tibet, Qinghai, and Ningxia) to grassland and agricultural areas (i.e., Shanxi, Liaoning, Hebei, Shandong, and Jilin Provinces), and the southern provinces became increasingly affected (Figures 4, 6) (14,17). This reemergence and the geographic expansion might be attributed to a variety of contributing factors.

Because brucellosis is not transmitted among humans, humans can be a sentinel for livestock brucellosis. For every human brucellosis case, 15 *B. melitensis* cases are expected in small ruminants or 150 *B. abortus* cases in cattle (37), and the large population of reservoir animals infected

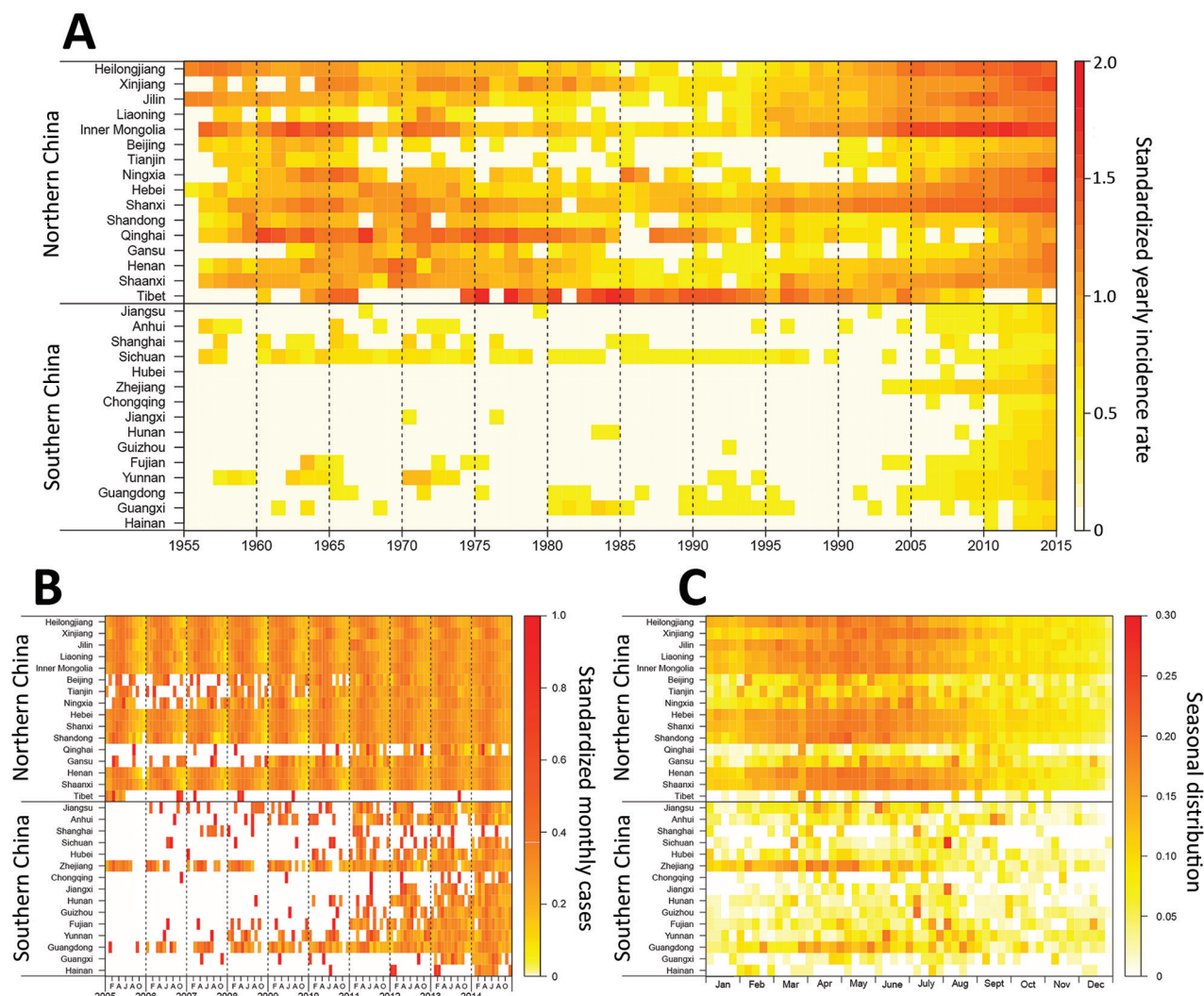
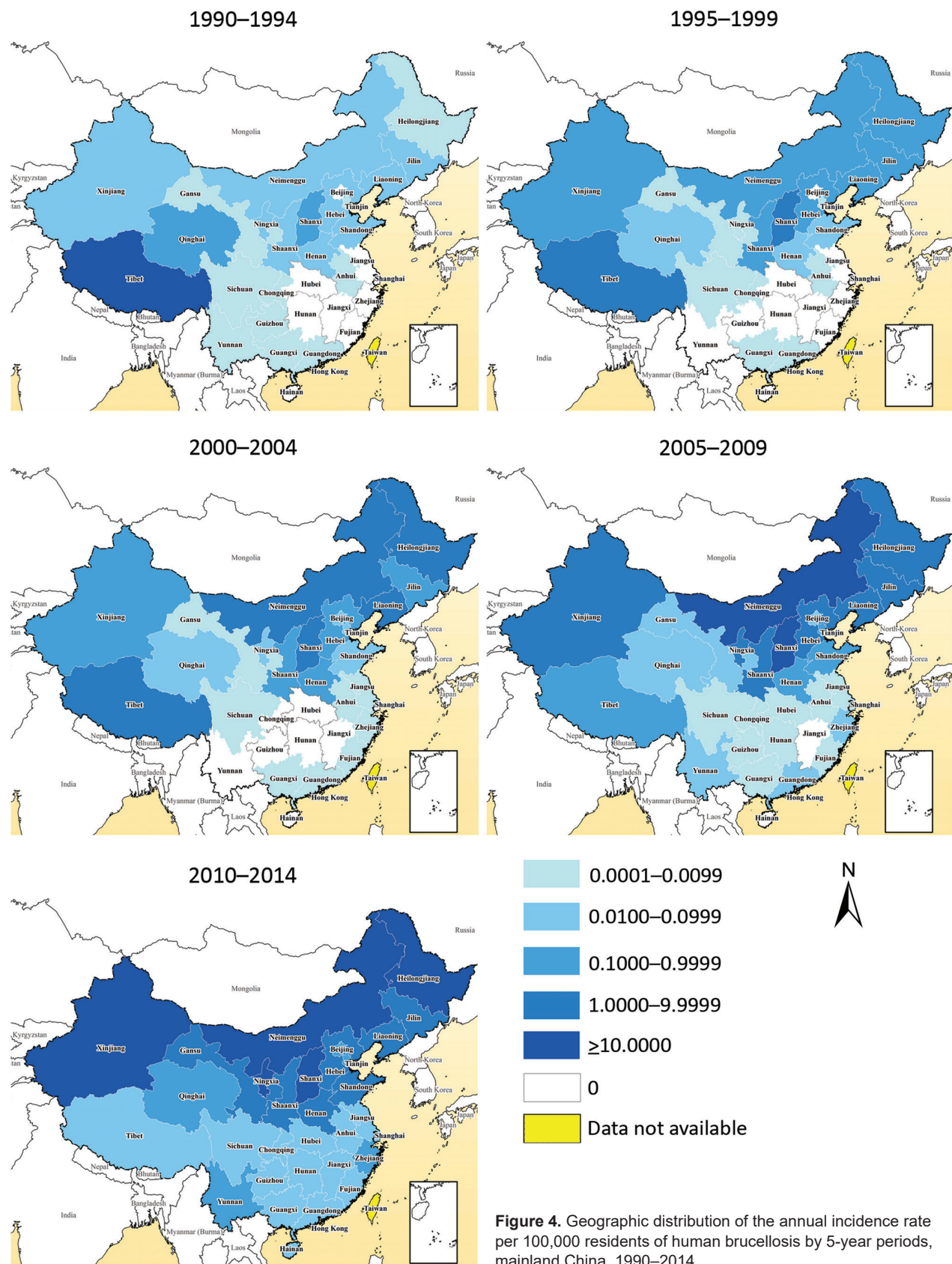


Figure 3. Heat map of provinces with human brucellosis cases, by north and south and the latitude of the capital city of each province, China. A) Time series of incidence rate per 100,000 residents during 1955–2014, standardized by the eighth root. B) Time series of monthly cases, 2005–2014, standardized by the annual number of cases reported by each province. C) Seasonal distribution of cases by province, plotted as the mean value of the proportion of cases in each week of the year from 2005 through 2014.



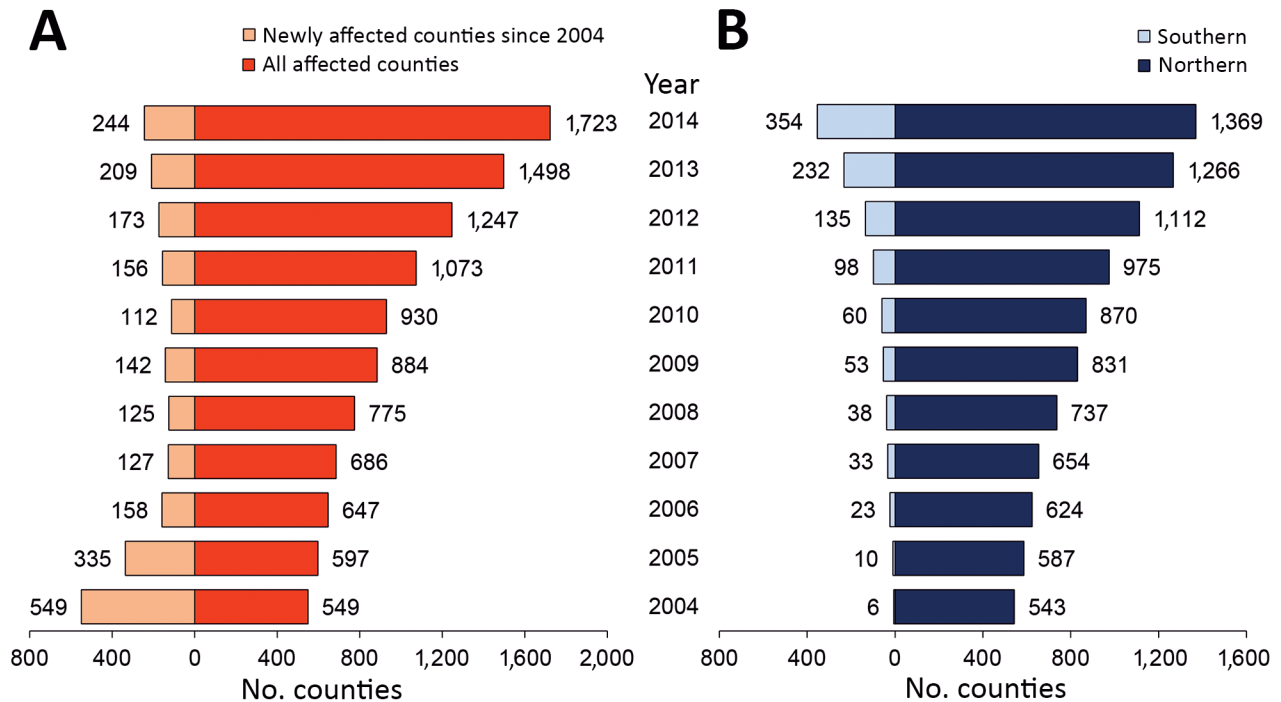


Figure 5. Number of counties with human brucellosis cases, mainland China, 2004–2014. A) Total number of affected counties each year and number of newly affected counties since 2004. B) Total number of affected counties each year in northern and southern China.

with *Brucella* spp. provides a source and is likely to be one of the main causes of infection for humans. The number of livestock dramatically increased during the past 3 decades to meet the growing demand for meat in China (e.g., the yearly numbers of cattle for meat production increased from 3.3 million in 1980 to 46.7 million in 2011, and numbers of sheep and goats increased 6-fold) (38), which would have resulted in an increase of the total population of infected animals, even with low-level constant seroprevalence in livestock. The spatial distribution of human brucellosis apparently overlaps with livestock density, especially high densities of sheep and goats (Figure 6), and high incidences of human brucellosis tended to occur most commonly in grasslands at moderate elevation, where sheep and goats are the predominant livestock (17,39). Another possible reason for the reemergence is the lack of vaccination, quarantine, and elimination of infected animals among backyard livestock. Moreover, the intensive modes of production, which accounted for the rearing of only 42.9% of cattle and 51.1% of sheep and goats in 2011, along with poor infrastructure and lack of high-standard and standardized protocols for maintaining good hygiene within the production cycle, might also result in increasing infections (38). Hence persons engaged in livestock husbandry, production, and trade are at high risk for brucellosis infection because of occupational exposure. Additionally, animal products supplied from brucellosis-endemic areas that have not undergone quarantine or pasteurization might increase the risk for

infection in nonoccupational populations and urban settings, taking a longer time from illness to diagnosis for imported cases in southern China, which might create extra challenges for disease prevention and case management (19,20,40). Therefore, susceptible livestock animals as the host and infection source for human infections are key to brucellosis prevention and control.

Vaccination is an effective method to reduce brucellosis incidence in livestock and correlates to a decrease in reported human cases, although no vaccines are available for humans (37,41). Compared with those from other countries, new sequence types of *Brucella* strains have been found in China, and the predominant biovars and sequence types of *Brucella* strains has changed during past half century in some regions (42). Thus, new livestock vaccines different from those recommended by the International Office of Epizootics are needed in China.

Targets have been set for brucellosis control in animals in 2015 and 2020 to reach the standard of control and decontamination by province (online Appendix Table 7) (25). However, to achieve the targets for brucellosis reduction, improvements are needed in socioeconomic parameters, diagnostic and notification systems in animals and humans, and the high prioritization for eliminating the disease in livestock. The continuing existence of human (and animal) brucellosis in China, with potential for further increases in incidence, indicates that the control of brucellosis will not be an easy task without taking a One Health approach,

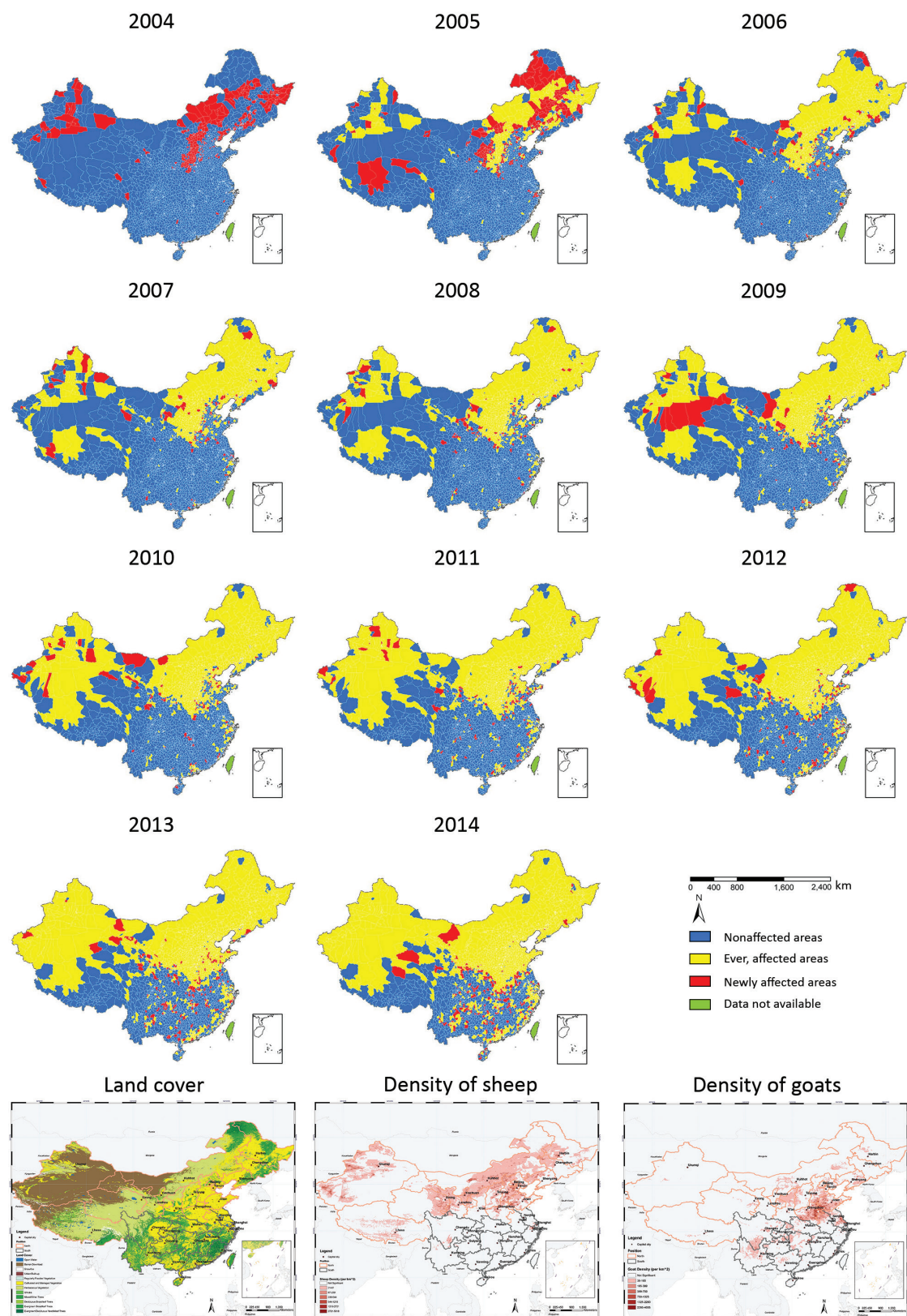


Figure 6. Geographic expansion of human brucellosis across counties and distribution of land covers (28) and density of sheep and goats (29), mainland China, 2004–2014.

integrating health professionals from the human and animal sectors and administrations. This effort extends beyond medical and veterinary duties and encompasses economic and even political factors (2).

Our study has some limitations. First, the data used were collected from passive public health surveillance that might be influenced by changes in surveillance protocols, such as modifications in case definitions and laboratory tests, reporting methods, and availability of health facilities and laboratory diagnostics over the years (online Technical Appendix Table 4). Second, individual case data were not reported before 2004, so demographic characteristics, laboratory confirmation, and case distribution could be analyzed only for 2004–2014. Third, data on *Brucella* strains and biotypes and on the varied clinical presentations, including asymptomatic brucellosis infections among humans, were unavailable in this study to explore the distribution of pathogens and the severity of disease. However, the data we used were the most nationally comprehensive for human brucellosis in China.

In view of the reemergence of brucellosis in mainland China and the high incidence, further studies should be conducted to explore the drivers of this situation during the past 2 decades. Livestock–human seroprevalence surveys are needed to understand the correlation between livestock and human brucellosis, to identify the most important animal host species, and to attempt to regress human seroprevalence to livestock prevalence or simply livestock numbers (43). The application of spatial–temporal transmission modeling, linking environmental and socioeconomic variables and density (e.g., <http://www.worldpop.org>) and mobility of livestock and humans (44) with the seroprevalence data, would improve understanding of the factors driving reemergence of brucellosis and enable us to better predict the risk in space and time. This information could further inform on potential causes of reemergence (45,46) and the economics of control in relation to ongoing control activities in China.

In summary, on the basis of notifiable surveillance data in mainland China during 1955–2014, we found that human brucellosis has reemerged since the mid-1990s, and the affected areas have expanded from northern to southern China, especially since 2004. Control strategies in animals and humans should be adjusted to account for these changes by adopting a One Health approach at different levels. Further research is warranted to explore the drivers behind the reemergence.

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Changing Epidemiology of Human Brucellosis, China, 1955–2014

Technical Appendix

Technical Appendix Table 1. Summary of laws or regulations related to brucellosis surveillance and control, China, 1955–2014*

No	Title	Approved by	Issued by	Period enforced	Note
1	The Administrative Measures of Infectious Disease	The State Council, PRC, on 1955 Jun 1	The Ministry of Health, PRC on 1955 Jul 5	1955 Jul 5–1978 Sep 19	Undulant fever (brucellosis) was 1 of the 18 notifiable infectious diseases
2	The National Programme of Agricultural Development (1956–1967)	The National People's Congress, PRC, on 1960 Apr 10 (proposed on 1956 Jan 23)	The National People's Congress, PRC on 1960 Apr 10	1956–1967	Brucellosis was 1 of diseases for control and elimination, targeted by the Leading Group of Endemic Diseases Prevention and Control in Northern, the CPC Central Committee, established in 1960
3	The Administrative Regulation of Acute Infectious Disease	The State Council, PRC	The Ministry of Health, PRC on 1978 Sep 20	1978 Sep 20	Brucellosis was 1 of the 25 notifiable infectious diseases
4	The Tentative Measures of Brucellosis Control and Prevention	The State Council, PRC on 1979 Dec 22	The Ministry of Health and the Ministry of Agriculture, PRC, on 1980 Jan 31	1980 Mar 1–current	
5	The Law on Infectious Disease Control and Prevention	The Standing Committee of the National People's Congress, PRC, on 1989 Feb 21 and revised on 2004 Aug 28		1989 Sep 1–2004 Nov 30; the revised version during 2004 Dec 1–current	Brucellosis was 1 of the 35 notifiable infectious diseases and listed in Category B (the revised version comprised 37 notifiable diseases)

6	The Implementing Measures of the Law on Prevention and Control of Infectious Diseases	The State Council, PRC, on 1991 Oct 4	The Ministry of Health, PRC, on 1991 Dec 6	1991 Dec 6–current	Brucellosis was listed as the Category B of pathogens for storage, carrying and transport
7	The Regulation on Disease Prevention and Control of Livestock and Poultry	The State Council, PRC, on 1985 Feb 14	The State Council, PRC, on 1985 Jul 1	1985 Jul 1–1997 Dec 31	Brucellosis was 1 of the Category B animal diseases
8	The Implementing Measures of the Regulation on Disease Prevention and Control of Livestock and Poultry	The Ministry of Agriculture, PRC, on 1985 Aug 7; the revised version approved by the 6th Standing Meeting of the Ministry of Agriculture, PRC, in 1991	The Ministry of Agriculture, PRC, on 1985 Aug 7 and revised version issued on 1992 Apr 8	1985 Aug 7–1992 Apr 7; the revised version during 1997 Apr 8–Dec 31	
9	The Law on Disease Prevention and Control of Livestock and Poultry	The Standing Committee of the National People's Congress, PRC, on 1997 Jul 3 and revised on 2007 Aug 30		1998 Jan 1–2007 Dec 31; the revised version during 2008 Jan 1–current	
10	The National Mid- and Long-term Plan of Animal Disease Control and Prevention, 2012–2020	The General Office of State Council, PRC, on 2012 May 20			Brucellosis was 1 of 16 prior domestic animal diseases for control

*CPC, Communist Party of China; PRC, People's Republic of China.

Technical Appendix Table 2. Variables in the aggregated dataset of human brucellosis cases, by year, China, 1955–2003

Variables*	Aggregated	Period
Total cases and no. fatalities	By month at national level	1955–2003
	By province	1955–2003
	By province and month	1980–2003
	By patient sex	1988–1997
		1999–2003
	By age group (each year <10 years of age, each 5-year from 10 to 85 years, and ≥85 years)	1988–1997
		1999–2003
Incidence rate and death rate (per 100,000 residents)	By occupation	1992–2003
	At national level	1955–2003
	By province	1955–2003
The case-fatality rate	At national level	1955–2003
	By province	1980–2003
No. counties with cases	At national level	1994–2003
No. cases imported from other province	At national level	1997–2003

*The data were aggregated and reported monthly by each province in mainland China, 1955 – 2003.

Technical Appendix Table 3. Variables in the individual dataset of human brucellosis cases, mainland China, 2004–2014

Variable*	Definition/classification	Completeness
Identification	A unique 8-digital number for each case.	100% reported
Sex	Male and female	100% reported
Age	Interval from the date of birth to date of onset	100% reported
Zone code of address	Unique 6-digital number at county level	100% reported
Indigenous or imported case	1. Reported by the same county 2. Imported from other county in the same prefecture 3. Imported from other prefecture in the same province 4. Imported from other province	100% reported
Nationality	Chinese or foreigner	100% reported
Occupation	Occupation/status of case-patients	99.5% reported
Type of diagnosis	Probable case (clinical diagnosed case) Confirmed case (laboratory-confirmed case)	100% reported
Date of onset	Date of illness onset	100% reported
Date of diagnosis	Date of diagnosis as a probable or confirmed case	100% reported
Date of report	First date of reporting to dengue surveillance system	100% reported
Date of death	Date of case-patient death, if applicable.	100% reported

*The data were reported by doctors within 24 hours after diagnosis to the online national Notifiable Infectious Disease Reporting Information System (NIDRIS) since 2004. NIDRIS enables all the healthcare institutes across the country to report individual cases of human brucellosis rapidly through the Internet to the data center located in the Chinese Center for Disease Control and Prevention.

Technical Appendix Table 4. Summary of diagnosis criteria and classification for human brucellosis, mainland China*

Variable	1977 Sep–1988 Sep	1988 Oct–1996 Jun	1996 Jul–2007 Oct	2007 Oct–current
Criteria or guidelines	<ul style="list-style-type: none"> • Tentative Criteria of Diagnosis and Treatment for Human Brucellosis • Tentative Rule of Criteria of Control Zone for Brucellosis and Evaluation Methods at County Level 	<ul style="list-style-type: none"> • Criteria of Diagnosis, Epidemic Area and Control Zone for Brucellosis • Tentative Guidelines for National Brucellosis Sentinel Surveillance 	<ul style="list-style-type: none"> • Diagnostic Criteria and Principles of Management for Human Brucellosis (GB 15988-1995) • Surveillance Standard for Brucellosis (GB16885-1997) • Guidelines for Human Brucellosis Surveillance (2005) 	<ul style="list-style-type: none"> • Diagnostic Criteria for Brucellosis (WS 269-2007) • Guidelines for Diagnosis and Treatment of Human Brucellosis (2012)
Issued by	The Leading Group Office of Endemic Diseases Prevention and Control in Northern (1960–1986), the CPC Central Committee, PRC	The Ministry of Agriculture and the Ministry of Health, PRC	The State Bureau of Technical Supervision, and the Ministry of Health, PRC	The Ministry of Health, PRC
Date issued	1977 Sep and 1981, respectively	1988 Oct 25 and 1990, respectively	1996 Jan 23, 1997 Jun 16, and 2005 Jul 26, respectively	2007 Apr 17 and 2012 Oct 8, respectively

Variable	1977 Sep–1988 Sep	1988 Oct–1996 Jun	1996 Jul–2007 Oct	2007 Oct–current
Date enforced	1977 Sep and 1981, respectively	25 October 1988 and 1990 respectively	1996 Jul 1, 1998 Jan 1, and 2005 Jul 26, respectively	2007 Oct 15 and 2012 Oct 8, respectively
Compared to previous criteria or guidelines	This the first criteria for human brucellosis issued in China	An updated version of previous criteria (left): revised the diagnosis and added the diagnosis criteria of brucellosis in animals	National standards based on previous criteria (left), including the specifications of the laboratory tests for human brucellosis	Based on previous criteria (left), the new national standard and guideline improve the diagnosis and case classification and laboratory tests
Epidemiologic linkage	1.1 Before the onset of illness, the case-patient had a history of close contact with suspected/confirmed animal cases, contaminated animal products, or cultures of <i>Brucella</i> spp.; or living in brucellosis-endemic areas; or closely connected with the produce, use, and research of vaccine of <i>Brucella</i> spp.			
Clinical description	2.1 Present with undulant, continued, intermittent, or irregular fever (including low fever) of variable duration (some days or weeks), with profuse sweating, fatigue, muscle pain, arthralgia, etc. Lymphadenia, splenomegaly, and hepatomegaly, Orchitis and epididymitis are common, but small numbers of patients may have jaundice and a variety of rashes; osteoarticular complications are common in patients at chronic phase.			
Laboratory tests	<p>3.1 Presumptive diagnosis</p> <ul style="list-style-type: none"> • Positive results of plate agglutination test or Bengal plate agglutination test: 0.03 mL serum (++) (criteria used since 1988); or 0.02 mL serum (++) (criteria used during September 1977– September 1988). • Intradermal allergic reaction test by 0.1 mL brucellin: skin redness and infiltration range ≥ 2.0 cm \times 2.0 cm or 4.0 cm² observed at 24 h or 48 h (since July 1996); or ≥ 2.5 cm \times 2.5 cm or 6.25 cm² observed at 24 h or 48 h (during October 1988–June 1996); or ≥ 2.5 cm \times 2.5 cm observed at 48 h (during September 1977–September 1988). <p>3.2 Serologic diagnosis</p> <ul style="list-style-type: none"> • Standard tube agglutination test: $\geq 1:100^{++}$ in titer; or $\geq 1:50^{++}$ in titer for the patient with course over 1 year (since October 2007); or ≥ 4-fold rise in titer in the paired serum samples after 2–4 weeks of the first test $\geq 1:100^{++}$ in titer of the patients with a history of <i>Brucella</i> vaccination within half year (since July 1996). • Complement fixation test: $\geq 1:10^{++}$ in titer. • Coomb's test: $\geq 1:400^{++}$ in titer (since October 1988); $\geq 1:200^{++}$ in titer (during September 1977–September 1988). • Cysteine test: $\geq 1:25^{++}$ in titer (used only during September 1977–September 1988). <p>3.3 Isolation of <i>Brucella</i> spp. from blood or other clinical specimen.</p>			
Diagnosis and classification	<p>4.1 Probable case: a patient with item 1.1 and 2.1.</p> <p>4.2 Confirmed case: a probable case with at least 1 positive result of item 3.1–3.3.</p>	<p>4.1 Probable case: a patient with item 1.1, 2.1, and 3.1.</p> <p>4.2 Confirmed case: a probable case with at least 1 positive result of item 3.2 or 3.3.</p>	<p>4.1 Probable case: a patient with item 1.1, 2.1, and 3.1.</p> <p>4.2 Confirmed case: a probable case with at least 1 positive result of item 3.2 or 3.3.</p>	<p>4.1 Suspected case: a patient with item 1.1 and 2.1.</p> <p>4.2 Probable case: a suspected case with at least 1 positive result of item 3.1.</p> <p>4.3 Confirmed case: a suspected or probable case with at least 1 positive result of item 3.2</p>

Variable	1977 Sep–1988 Sep	1988 Oct–1996 Jun	1996 Jul–2007 Oct	2007 Oct–current
				or 3.3.
				4.4 Latent infection: a person with item 1.1 and at least 1 positive result of item 3.2 or 3.3, but without item 2.1.

*There were not criteria/guidelines for human brucellosis diagnosis issued by the Chinese national health authorities during 1950–1976, but human brucellosis cases are diagnosed by clinical manifestations, epidemiologic links, and/or available laboratory tests at that time including intradermal allergic reaction test, agglutination test and culture, and so on. CPC, Communist Party of China; GB, Guo-Biao (National Standard); PRC, People's Republic of China; WS, Wei-Sheng (Standard in Public Health).

Technical Appendix Table 5. Summary of the geography of each province in mainland China

No.	Province	Zone code	Climate*	Inland or coastal province	Northern or southern*	Adjacent country	Capital city	Latitude†	Longitude
1	Heilongjiang	230000	Mid-temperate	Inland	Northern	Russia	Harbin	46.1138	126.185
2	Jilin	220000	Mid-temperate	Inland	Northern	Russia and North Korea	Changchun	44.1156	125.352
3	Xinjiang	650000	Mid-temperate	Inland	Northern	Russia, Mongolia, Kazakhstan, Kyrgyzstan, Tajikistan, Afghanistan, Pakistan, and India	Urumqi	43.7878	87.574
4	Inner Mongolia	150000	Mid-temperate	Inland	Northern	Russia and Mongolia	Hohhot	40.7632	110.82
5	Liaoning	210000	Warm-temperate	Coastal	Northern	North Korea	Shenyang	40.6843	122.589
6	Beijing	110000	Warm-temperate	Inland	Northern	None	Beijing	39.94	116.41
7	Tianjin	120000	Warm-temperate	Coastal	Northern	None	Tianjin	39.16	117.2
8	Hebei	130000	Warm-temperate	Coastal	Northern	None	Shijiazhuang	38.1269	115.078
9	Shanxi	140000	Warm-temperate	Inland	Northern	None	Taiyuan	37.8098	112.8
10	Ningxia	640000	Mid-temperate	Inland	Northern	None	Yinchuan	37.6234	106.026
11	Qinghai	630000	Cold	Inland	Northern	None	Xining	36.6401	101.835
12	Shandong	370000	Warm-temperate	Coastal	Northern	None	Jinan	36.313	118.368
13	Gansu	620000	Mid-temperate	Inland	Northern	Mongolia	Lanzhou	35.5751	104.657
14	Henan	410000	Warm-temperate	Inland	Northern	None	Zhengzhou	34.707	113.058
15	Shaanxi	610000	Warm-temperate	Inland	Northern	None	Xi'an	34.3038	108.849
16	Tibet	540000	Cold	Inland	Northern	India, Bhutan, Nepal, Myanmar, and Pakistan	Lhasa	29.65	91.13
17	Jiangsu	320000	Subtropical	Coastal	Southern	None	Nanjing	32.8614	118.575
18	Anhui	340000	Subtropical	Inland	Southern	None	Hefei	31.8527	117.543
19	Shanghai	310000	Subtropical	Coastal	Southern	None	Shanghai	31.28	121.46
20	Hubei	420000	Subtropical	Inland	Southern	None	Wuhan	30.8781	112.606
21	Sichuan	510000	Subtropical	Inland	Southern	None	Chengdu	30.2459	103.978
22	Zhejiang	330000	Subtropical	Coastal	Southern	None	Hangzhou	29.9769	120.444

23	Chongqing	500000	Subtropical	Inland	Southern	None	Chongqing	29.59	106.55
24	Jiangxi	360000	Subtropical	Inland	Southern	None	Nanchang	28.2274	115.261
25	Hunan	430000	Subtropical	Inland	Southern	None	Changsha	27.3878	113.006
26	Guizhou	520000	Subtropical	Inland	Southern	None	Guiyang	27.3627	106.816
27	Fujian	350000	Subtropical	Coastal	Southern	None	Fuzhou	25.337	118.827
28	Yunnan	530000	Subtropical	Inland	Southern	Vietnam, Laos, and Myanmar	Kunming	24.8119	103.034
29	Guangdong	440000	Subtropical	Coastal	Southern	None	Guangzhou	22.9286	113.414
30	Guangxi	450000	Subtropical	Coastal	Southern	Vietnam	Nanning	22.85	108.37
31	Hainan	460000	Tropical	Coastal	Southern	None	Haikou	19.5855	110.101

*The general climate of each province, which is available on the website of China Meteorological Administration (<http://www.cma.gov.cn/>). Each province is categorized as temperate northern province (16 provinces) or subtropical southern province (15 provinces) from previous study (Feng L, et al. Influenza-associated mortality in temperate and subtropical Chinese cities, 2003-2008. Bull World Health Organ. 2012;90:279–88).

†The latitude and longitude of capital city of each province.

Technical Appendix Table 6. Demographic and epidemiologic characteristics of human brucellosis cases, mainland China, 2004–2014*

Characteristic	Total, N = 346,682	Male, n = 258,238	Female, n = 88,444
Type of case			
Confirmed	314,694 (90.8)	233,615 (90.5)	81,079 (91.7)
Probable	31,988 (9.2)	24,623 (9.5)	7,365 (8.3)
Age, y			
Median (IQR)	44.0 (34.1–53.9)	43.9 (34.0–53.7)	45.0 (35.0–54.0)
Age group			
0–4	2,424 (0.7)	1,446 (0.6)	978 (1.1)
5–14	6,638 (1.9)	4,401 (1.7)	2,237 (2.5)
15–24	25,262 (7.3)	19,800 (7.7)	5,462 (6.2)
25–34	57,651 (16.6)	44,407 (17.2)	13,244 (15)
35–44	90,777 (26.2)	68,185 (26.4)	22,592 (25.5)
45–54	87,566 (25.3)	63,824 (24.7)	23,742 (26.8)
55–64	57,274 (16.5)	41,837 (16.2)	15,437 (17.5)
≥65	19,090 (5.5)	14,338 (5.6)	4,752 (5.4)
Year of onset			
2004	11,477 (3.3)	8,818 (3.4)	2,659 (3.0)
2005	18,416 (5.3)	13,972 (5.4)	4,444 (5.0)
2006	19,014 (5.5)	14,359 (5.6)	4,655 (5.3)
2007	19,723 (5.7)	14,773 (5.7)	4,950 (5.6)
2008	27,771 (8.0)	20,672 (8)	7,099 (8.0)
2009	35,824 (10.3)	26,421 (10.2)	9,403 (10.6)
2010	33,786 (9.7)	24,822 (9.6)	8,964 (10.1)
2011	38,183 (11.0)	28,552 (11.1)	9,631 (10.9)
2012	39,607 (11.4)	29,869 (11.6)	9,738 (11.0)
2013	44,739 (12.9)	33,068 (12.8)	11,671 (13.2)
2014	58,142 (16.8)	42,912 (16.6)	15,230 (17.2)
Month of onset			
January	22,315 (6.4)	16,898 (6.5)	5,417 (6.1)
February	26,571 (7.7)	20,585 (8.0)	5,986 (6.8)
March	37,061 (10.7)	28,451 (11.0)	8,610 (9.7)
April	43,402 (12.5)	33,203 (12.9)	10,199 (11.5)
May	49,472 (14.3)	37,488 (14.5)	11,984 (13.5)
June	45,588 (13.1)	33,788 (13.1)	11,800 (13.3)
July	37,827 (10.9)	27,390 (10.6)	10,437 (11.8)
August	27,659 (8.0)	19,840 (7.7)	7,819 (8.8)
September	16,786 (4.8)	11,880 (4.6)	4,906 (5.5)
October	14,677 (4.2)	10,416 (4.0)	4,261 (4.8)
November	13,555 (3.9)	9,738 (3.8)	3,817 (4.3)
December	11,769 (3.4)	8,561 (3.3)	3,208 (3.6)
Median delay, d (IQR)			
From illness onset to diagnosis	20.0 (7.5–42.0)	20.0 (7.7–42.0)	19.8 (6.8–42.6)

Characteristic	Total, N = 346,682	Male, n = 258,238	Female, n = 88,444
From diagnosis to report	0.25 (0.04–0.65)	0.24 (0.04–0.65)	0.25 (0.04–0.65)
From illness onset to report	20.6 (7.8–43.4)	20.7 (8.4–43.3)	20.5 (7.4–43.6)
Where were the cases imported from			
The same county	205,941 (59.4)	153,231 (59.3)	52,710 (59.6)
Other county of same prefecture	92,351 (26.6)	68,584 (26.6)	23,767 (26.9)
Other prefecture of same province	32,584 (9.4)	24,415 (9.5)	8,169 (9.2)
Other province	15,806 (4.6)	12,008 (4.6)	3,798 (4.3)

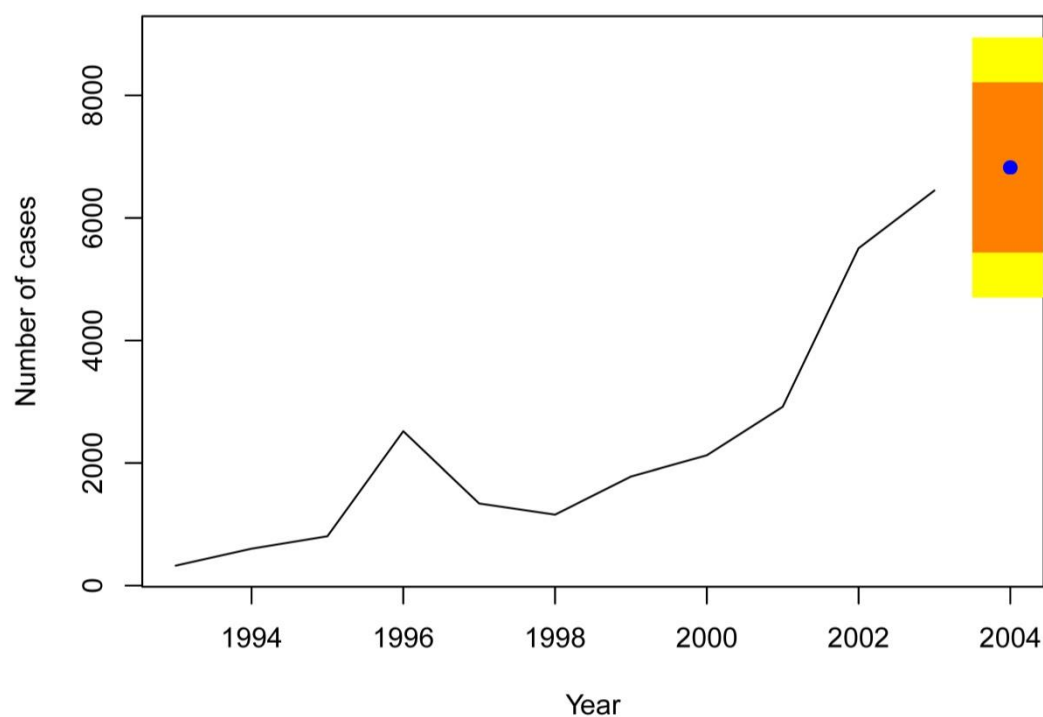
*Data are presented as no. (%) patients unless otherwise indicated. IQR, interquartile range.

Technical Appendix Table 7. Summary of standard of brucellosis control, mainland China

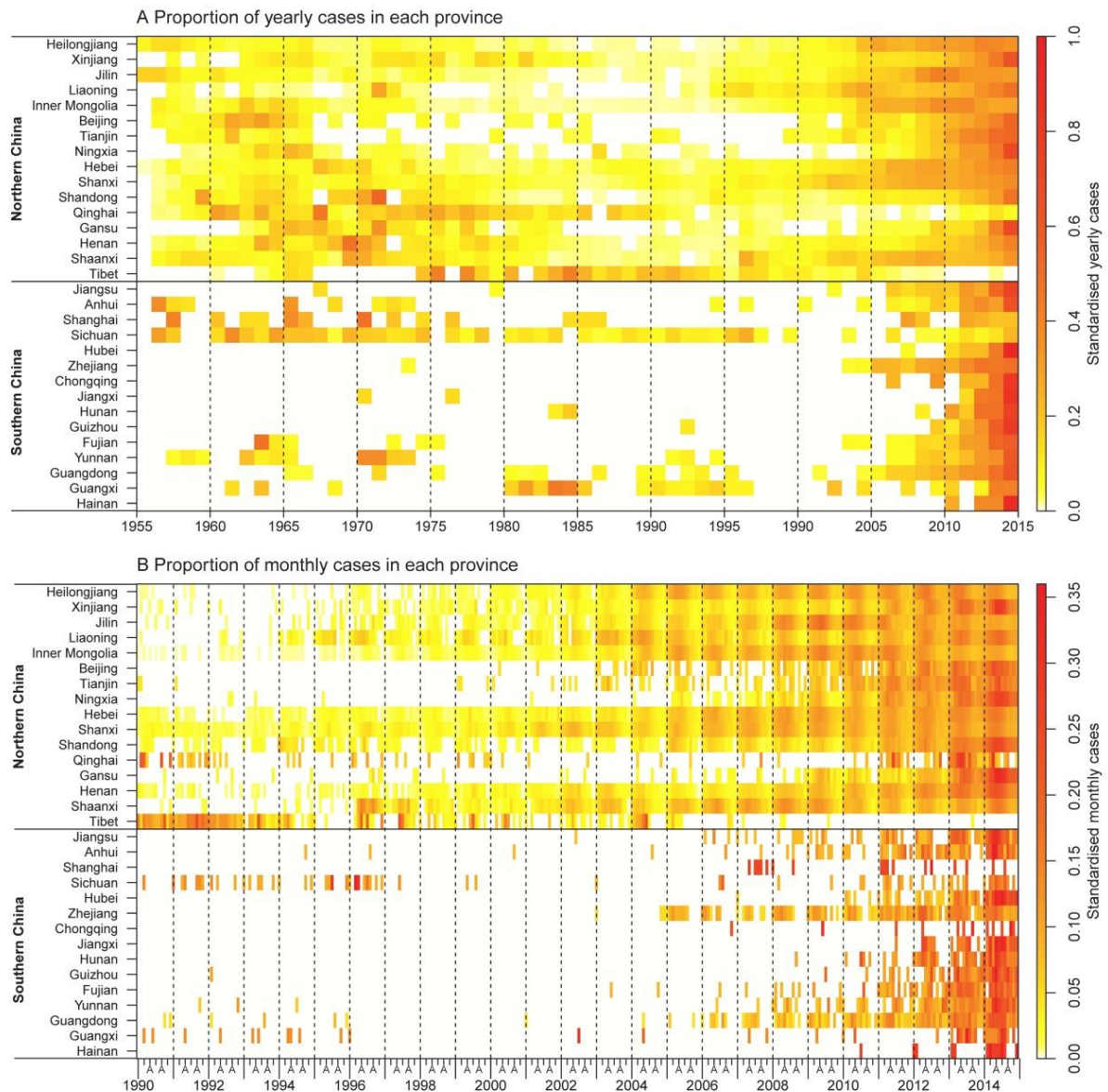
County-level category	Criteria*
Criteria of control area	<p>Meeting the following 3 requirements at least 2 consecutive years:</p> <ol style="list-style-type: none"> 1. For livestock vaccinated >18 months of age or without vaccination, sampling >3,000 serum samples in pastoral areas, >1,000 serum samples in agricultural areas and semiagricultural and semipastoral areas, and detected by tube agglutination test (seropositive <0.5% for sheep, goats, and deer, <1% for cattle, and <2% for pigs) or complement fixation test (<0.5%). 2. Sampling >200 (total) abortion specimens from sheep, goats, cattle, and pigs (if the number of abortions is insufficient, sampling normal placenta, breast milk, vaginal secretions, or spleen), and without <i>Brucella</i> spp. detected. 3. All animals infected with <i>Brucella</i> have been culled with biosafety disposal.
Criteria of stable control area	<p>Meeting the following 3 requirements at least 3 consecutive years using the same requirement of sampling and laboratory tests in the criteria of control area:</p> <ol style="list-style-type: none"> 1. Seropositive <0.1% for sheep or goats, <0.3% for pigs, <0.2% for cattle and deer. 2. No <i>Brucella</i> detected from specimens of sheep, goats, cattle, and pigs. 3. All animals infected with <i>Brucella</i> have been culled with biosafety disposal.
Criteria of decontaminated area	<p>Meeting the following 2 requirements at least 2 consecutive years using the same requirement of sampling and laboratory tests in the criteria of control area:</p> <ol style="list-style-type: none"> 1. No outbreak of brucellosis within 2 years after meeting the criteria of stable control area. 2. All specimens are negative by tube agglutination test or complement fixation test.

*The Ministry of Agriculture, People's Republic of China. Technical specification of brucellosis control and prevention. 2006 [cited 2015 Aug 28].

<http://www.moa.gov.cn/zwllm/nybz/200803/P020080429675112156434.doc>



Technical Appendix Figure 1. Prediction value (6,823) for the number of human brucellosis cases in 2004 by the Holt's exponential smoothing method. The 80% CIs (orange) and 95% CIs (yellow) of the prediction value are 5,436–8,211 and 4,701–8,945 cases respectively. Comparing to this upper limited value (8,945) of the 95% CI, the actual number of cases (11,477) in 2004 has an excess proportion of 22.1%.



Technical Appendix Figure 2. Heat map of human brucellosis cases, by province, sorted by north and south and the latitude of capital city of each province, mainland China. A) Time series of the annual number of human brucellosis cases by province during 1955–2014, standardized by the total number of cases in each province. B) Time series of the monthly number of human brucellosis cases by province during 1990–2014, standardized by the total number of cases in each province.